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POLYMERIC MATERIALS

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IMMUNE MODULATING EFFECTS OF POLY(ICLC) IN MICE, MONKEYS AND MAN

1988

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The stabilized double stranded RNA, poly(ICLC), in addition to being an active interferon inducer, is able to modify a variety of humoral and cell associated immune activities in mice, monkeys and humans. In mice there is augmentation, *in vitro* and *in vivo* of macrophage activation and NK cell activity, as well as specific cytotoxic T cells. In primates, poly(ICLC) increases the amount and rapidity of formation of antibodies to a number of weak vaccines. In addition there is increased macrophage and 2'5' *A. synthetase* activities. At low doses there is an augmentation of NK cell action, but inhibition at higher doses. Increases in T4/T8 ratio were found. Lymphocyte subset populations are modified in different ways, depending on the dose. In general low doses augment the several immune actions much better than do the higher doses.

INTRODUCTION

This presentation will consist of two parts; the first will be a review of material that has been published and the second will summarize recent data dealing with cell associated hematological and immunological changes induced in monkeys and humans by poly(ICLC).

First a word about poly(ICLC). A number of years ago, interferon was thought of only in terms of a natural antiviral substance, with its effects on the immune system and as a cell growth inhibitor coming a good deal later. However, until recently, there was not enough IFN to do adequate antiviral trials in mice, let alone in humans, who would require much larger amounts. Investigators looked for non-replicating entities that would cause the host to produce large quantities of his own IFN. A number of such agents were found, the best of which was a ds-RNA containing one strand of poly(I) and one of poly(C). Poly(IC) is a good IFN inducer in mice, and is a good antiviral and antitumor agent in mice. However, when it was tried in primates, including humans, it induced very little interferon and had no antitumor action. It was shown that there is present in primate serum a high concentration of hydrolytic enzymes that
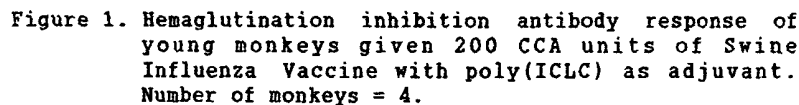
degrade and inactivate poly(IC), probably accounting for the lack of activity in monkeys, chimpanzees and people. A derivative of poly(IC) was prepared by adding poly 1-lysine and carboxymethylcellulose, poly(ICLC), which partially resists this hydrolysis, and which is capable of inducing good qualities of IFN in primates.[1]

RESULTS

The activity of poly(ICLC) as an antiviral agent is shown in Table 1, which lists some of the virus diseases that have been treated with poly(ICLC).[1] It was soon realized that poly(ICLC) was not just a poor man's IFN, readily available and relatively inexpensive, but it also had a number of immune modifying effects, which often were not the same as those induced by IFN itself. One area of difference between IFN and poly-(ICLC) is the fact that, by and large, IFN inhibits antibody production to an antigen or vaccine, while poly(ICLC) is an effective immune adjuvant with many but not all antigens.

Table 1. Virus diseases of animals that have been treated with poly(ICLC).

Disease	Animal	Results
Simian hemorrhagic fever	Monkey	Complete protection if given before virus, none if given after virus
Venezuelan equine encephalitis	Monkey	No animals with light virus challenge died; poly(ICLC) reduced viremia by 50%
Yellow fever	Monkey	75% protection up to 8 hr. post-challenge
Japanese encephalitis	Monkey	50% protection up to 24 hr. post-challenge
Tacaribe virus	Monkey	No effect by poly(ICLC)
Rabies	Monkey & mouse	See text
Hepatitis	Chimpanzee	Virus controlled while on drug. Control ends when treatment stopped
Bolivian hemorrhagic fever	Monkey	Possible worsening of disease
Tick-borne encephalitis	Monkey	Strong protection
Vaccinia	Monkey	Strong protection
Vaccinia skin lesions (topical treatment)	Rabbit	Spread of lesions stopped

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Figure 1. Hemaglutination inhibition antibody response of
young monkeys given 200 CCA units of Swine
Influenza Vaccine with poly(ICLC) as adjuvant.
Number of monkeys = 4.

Three examples of this effect follow. A subunit vaccine vs. Swine Flu
virus, is poorly effective in young people and in young monkeys. When
this vaccine is given along with a small dose of poly(ICLC), the
resultant antibody titer is elevated to the point where it would be
expected to be effective in disease prevention.[2] See Figure 1.

Another example is the polysaccharide vaccine against *Hemophilus
influenzae*. This agent causes serious disease in children, particularly
young children, where the vaccine has poor effectiveness. The vaccine is
also poorly effective in young monkeys. When low doses of poly(ICLC) is
given along with the vaccine to young monkeys the antibody response is
strongly augmented.[3] These results are summarized in Table 2.

The third example we will mention is the adjuvanticity of poly(ICLC)
with a killed vaccine against *Venezuelan Equine encephalitis* virus, which
is shown in Figure 2.[4] The upper part of this figure shows the production
of antibody to the vaccine without poly(ICLC). The vaccine was given
twice, as indicated. The lower part of the figure shows the increased,

Table 2. Effect of low doses of poly(ICLC) on antibody
production by Rhesus monkeys in response to a
polysaccharide vaccine for *hemophilus* *influenza*
antibody levels.*

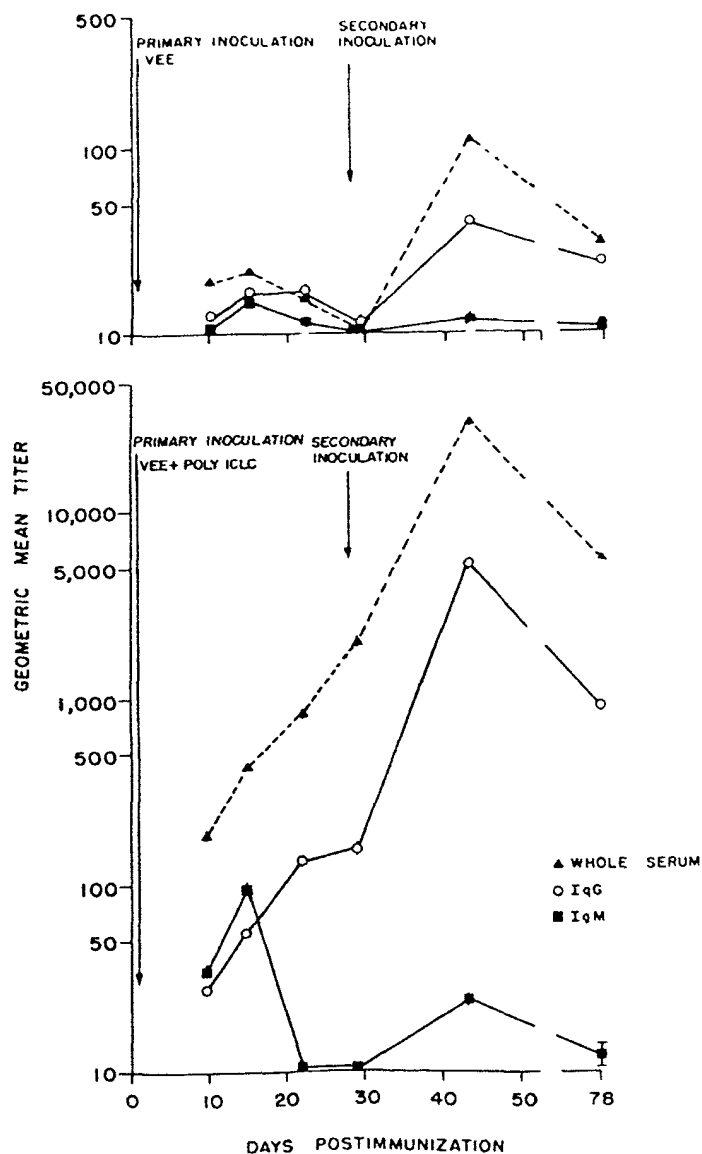| Treatment	Pre	Day 7	Day 14	Day 20	Day 28	Day 34	Day 42
Vaccine	100	590	348	286	225	187	113
Vaccine + poly(ICLC) 0.3 mg/kg	100	5643	5040	3340	2063	2182	780
Vaccine + poly(ICLC) 0.03mg/kg	100	6589	3904	1884	1132	839	721
* Normalized ng/ml.							

Figure 2. Adjuvant effect of poly(ICLC) in monkeys receiving
heat killed virus vaccine vs. *Venezuelan Equine
Encephalitis* Virus.

earlier response obtained when poly(ICLC) is given along with the
vaccine. A second dose of the vaccine, this time without poly(ICLC) leads
to the production of very high levels of antibody. The usual formation of
IgM followed by replacement with IgG, is not altered by poly(ICLC).

So far the data has dealt only with humoral immunity. Several
investigators have published observations about the effect of poly(ICLC)
on several cell-associated immune activities in mice.[5-7]

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Figure 3. Effect of poly(ICLC) on delayed type hyper-
sensitivity. Poly(ICLC) (10 micrograms) was
injected subcutaneously into mice previously
sensitized to sheep red blood cells (SRBC), on the
day indicated prior to rechallenge of mice with
SRBC. Four days after the rechallenge, footpad
swelling was measured.

Delayed Hypersensitivity (DTH)

When mice that have been sensitized to sheep red blood cells (SRBC)
are challenged in the foot pad with SRBC, there is a swelling of the
footpad. Figure 3 shows that poly(ICLC) given to mice already sensitized
to SRBC strongly enhanced foot pad swelling, when given any time between
3 days prior to the challenge up to the time of challenge.[5] This is a
strong contrast to what interferon does.[8] If IFN is given before the
challenge, a complete suppression of the DTH can occur. These differences
between IFN and poly(ICLC) may relate to the difference between the
effects of the two agents on colony forming cells and on production of
colony stimulating factor (CSF). Mouse granulocyte-macrophage precursor
cells can give rise to colonies if a glycoprotein, CSF is present. Poly-
(ICLC), both in vivo and in vitro augments colony formation, while IFN
either is inhibitory or has no effect.[5]

Table 3 shows that cultures of macrophages produce CSF when stim-
ulated by poly(ICLC) and by IFN. To end the CSF story, Figure 4 shows the
effect of antibody to IFN on the production of CSF by IFN and by

Table 3. Effect of IFN and poly(ICLC) on production by
macrophage of soluble products.

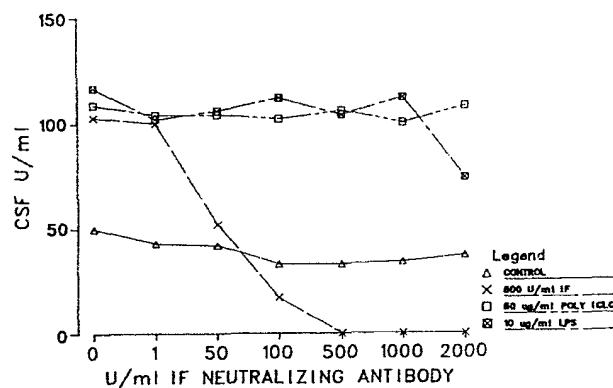| Agent	IFN Units	CSF Units	Prostaglandin E
Control	0	30	70
Poly ICLC 10 µg/ml	50	ND	1400
50 µg/ml	1000	120	2000
IFN 500 IU/ml	NA	100	225

Figure 4. Effect of antibody to interferon on indication of colony stimulating factor (CSF) in macrophage cultures by interferon and by poly(ICLC).

poly(ICLC). When Ab to INF is added to the culture where CSF is being induced by IFN the production of CSF is inhibited, but when Ab to IFN is added to the cells being stimulated by poly(ICLC) there is no inhibition of CSF production, suggesting that poly(ICLC) stimulates CSF production independently of the IFN produced.[5]

Exposure of the macrophage to very low doses of the drug, *in vitro* enhances peritoneal macrophage cytotoxicity vs. tumor cells, as shown in Table 4. When the drug is given i.v. to mice at 8 or 16 µg/mouse peritoneal macrophage cytotoxicity is also increased, as shown in Table 5.[6]

When given i.v. to mice, poly(ICLC) augmented natural killer cell activity in peritoneal cells, lungs and spleen. Figure 5 shows some typical results.[6] There are many biological response modifiers that can augment NK cell activity, after one or two treatments, but then they lose their effectiveness. Mice do not develop this refractoriness after treat-

Table 4. *In vitro* activation of macrophage cytotoxicity.

Concentration µg/ml	Percent Cytotoxicity	
	MBL-2	P815
0.001		2
0.005		21
0.05	62	
0.01		20
0.1	70	34
1.0	70	44
5.0	85	46
10.0	60	47

Ratio of macrophage to target cells; MBL-2 (10:1; P815 (10:1). Control values subtracted from experimental.
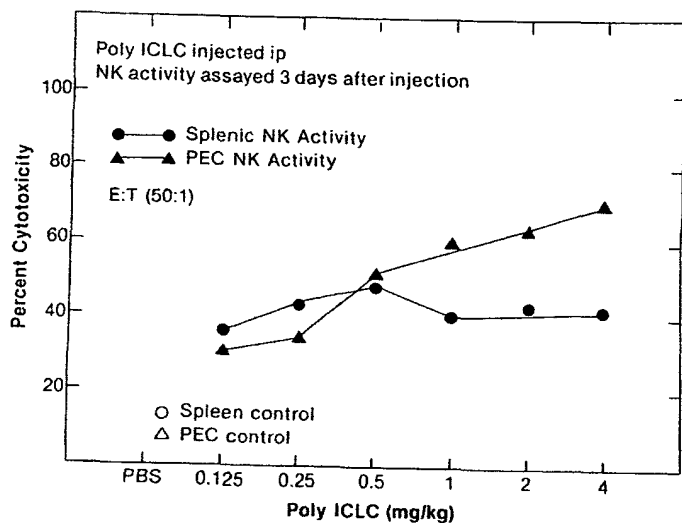
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Figure 5. Effect of injection of poly(ICLC) into mice on natural killer cell activity of peritoneal exudate cells and of spleen cells.

ment with poly(ICLC). It can be given twice weekly for quite a few weeks without a diminution in response. As mentioned later, they were boosted at low doses but not at higher ones.

One other activity that is enhanced by the agent in mice is the mixed lymphocyte reaction (MLR). If live spleen cells from C57B1 mice are co-cultivated with irradiated cells from C3H mice the live cells respond by increasing in growth rate, as measured by uptake of tritiated thymidine. If poly(ICLC) is added to the cell mixture during the cocultivation, in doses from 0.01 to 5 µg/ml., there is an increase in the MLR. At 10 µg/ml there was inhibition (6). These results are summarized in Table 6.

It also has been shown that when mice are vaccinated with irradiated tumor cells mixed with poly(ICLC), specific cytotoxic T cells are developed. The vaccine of irradiated tumor cells alone has little or no effect, as seen in Table 7.[7]

Table 5. *In vivo* activation of macrophage cytotoxicity.

Concentration Poly(ICLC) (mg/kg)	Percent Cytotoxicity Day of Observation		
	1	3	6
none	10	8	9
0.4	60	19	12
0.8	75	55	20

Mice received single i.p. treatment of either 0.4 or 0.8 mg/kg and peritoneal macrophages were harvested for assay 1, 3 or 6 days after treatment.

Table 6. Poly(ICLC) augmentation of spleen cell response in a mixed lymphocyte response (a).

µg/mL F5	C3H R(b) only	C3H+C57S(c)	S.I.(d)	S.I.(e)
Media	2,719	17,630	5.48	5.48
250.0	1,865	22,303	7.20	11.96
0.01	2,373	28,673	9.55	12.08
0.1	1,089	31,847	10.71	29.24
1.0	794	35,836	12.18	45.13
5.0	811	41,272	14.18	50.89
10.0	696	19,460	6.15	27.96

(a) Poly(ICLC) or Thymosin F5 was added to the culture at various concentrations. Media control was in the absence of BRM. The MLR was established using irradiated $C_{57}B1/6$ spleen cells as stimulator cell and C_3H spleen cells as responders at a suboptimal R:S ratio of 10:1. The cultures were pulsed on day 5 with 1 µCi ^{3}H-Thymidine for 24 hr. prior to harvest (N = 4).
(b) Responder C_3H spleen cells culture alone.
(c) C_3H spleen cells cultured with irradiated $C_{57}B1/6$ spleen cells.
(d) Stimulation index compared to media control.
(e) Stimulation index compared to drug control.

The net effect of these and possibly other immune modifications, is that poly(ICLC) can cause the regression and disappearance of small experimental tumors. However if the tumor is allowed to grow to a large size before initiation of treatment, the tumor mass must first be reduced by a cytocidal agent, like cytoxan, for the poly(ICLC) to be effective.[3]

Table 7. Immunoadjuvant activity of poly(ICLC) in a tumor challenge study (a).

Vaccine tumor cells	Adjuvant	µg/animal	Day 4, TB/total	(Cm^3)	Day 63 TB/total (Cm^3)
–	HBSS	0.05	5/5	(0.082)	5/5
UV-2237	HBSS		4/5	(0.147)	4/5
UV-2237	Thymosin F5	500	0/5	–	0/5
UV-2237	Poly(ICLC)	50	1/5	(0.110)	0/4

(a) Mice were immunized intradermally with a vaccine composed of collagenase-DNase dissociated tumor cells (1 x 10^6) suspended in either HBSS, thymosin F5 or Poly(ICLC). Tumor challenge was 9 days later using 2 x 10^5 UV-2237 tissue culture propagated tumor cells injected into a posterior footpad.

Table 8. Effects of adjuvants on survival of mice immunized
with vaccine to rift valley fever virus.*

Treatment		dose (μg/kg)	Percent survivors day 35 (N = 16)
Vaccine	Adjuvant		
Vaccine + Poly(ICLC)		20	50
		100	50
		200	13
Saline + Poly(ICLC)		200	6
Vaccine + Freund's complete adjuvant			6
Saline + Freund's complete adjuvant			6
Vaccine + Freund's incomplete adjuvant			6
Saline + Freund's incomplete adjuvant			0
Vaccine controls			19
Saline controls			0

In an experiment using a different type of endpoint, it was shown
that poly(ICLC), given together with a killed vaccine vs. RVF virus,
increases the survival of mice subsequently challenged with live RVF
virus. Again the higher dose of the drug has less beneficial effect than
does smaller doses, as summarized in Table 8.[9]

All the material presented so far has been a review of previously
published work. The second part of this presentation deals with unpub-
lished studies on hematological and cell associated immune modifications
induced in monkeys and people by poly(ICLC). Table 9 lists the names of
people who contributed to the work to be reported.

First, the data obtained in studies with monkeys will be given. Poly-
(ICLC) was injected, i.v., into 2 monkeys at two different dose levels
according to the following protocol. On day 0 blood was drawn for the
determination of several hematological and immunological parameters. The
first injection of poly(ICLC) was then given, i.v., at 0.2 mg/m². Then,
24 hours later (day 1) blood was drawn for the same battery of tests, and

Table 9. Names of people who were collaborators in the work
to be reported.

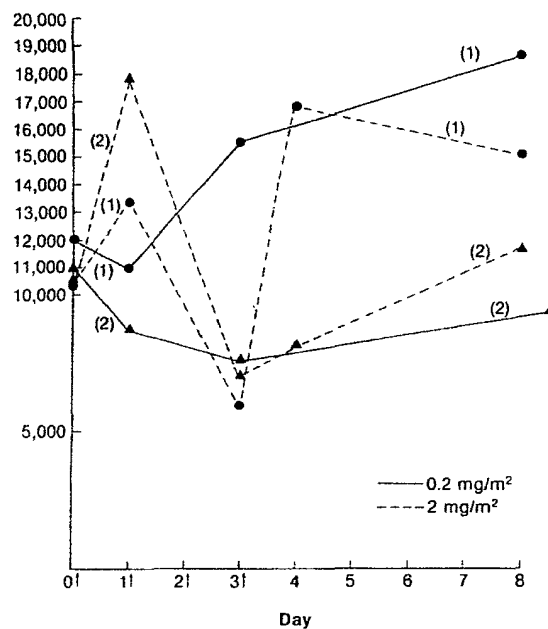|	
C. Bever	NINCDS
A. Malluish	NCI
D. McFarlin	NINCDS
H. MacFarland	NINCDS
A. Salazar	Walter Reed
R. Tyndall	U. Texas Med. Ctr., Dallas

Figure 6. Effect of repeated injection of poly(ICLC) into monkeys on total white blood cell numbers. Ordinate is number of WBC/mm³ of blood, abscissa is the numbers of days after injection. Arrows indicate injection days.
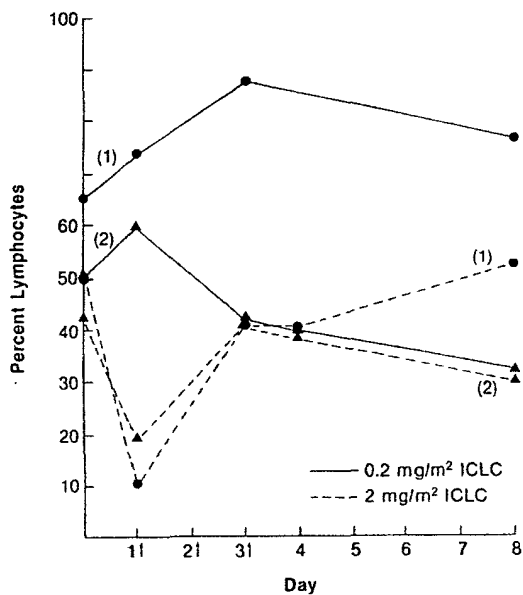

Figure 7. Effect of poly(ICLC) injection into monkeys on percent of lymphocytes in peripheral blood. Abscissa represents days after start. Arrows indicate injection times.

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another injection of the drug was given. The same procedure was done on days 2 and 3. On day 4 blood was drawn, but no drug was given. On day 8 blood was drawn again. The animals were not used again for 7 weeks and then the same procedure was repeated at a 10 fold higher drug level, 2.0 mg/m².

The data from the low dose of drug reveals that, while there is a large amount of fluctuation, there is a transient decrease in total wbc beginning on day 1, followed by a return to either normal or above by day 8. The higher dose leads to an increase on day 1, followed by a decrease to normal or slightly above by day 8, as shown in Figure 6.

The changes in composition of the different subsets of wbc are more informative than changes in total wbc. Figure 7 shows the changes in percent lymphocytes in the monkeys given the two levels of drug. At the lower level of drug, the % lymphocytes increased for a day or two, and then returned to normal, while at the higher level of drug, there was a transient (1.5 days) sharp lymphopenia, even though as shown in Figure 6 the total wbc increased, and then both returned to normal.

Since the great bulk of wbc consists of leukocytes and granulocytes, this means that with the high dose of drug there was a marked granulocytosis for 48 hours, with a return to normal, while at the lower dose there were only modest changes in granulocytes.

NK cell activity was modified differently at the two doses of drug. At the low dose there were either an initial drop or no change in NK activity, followed by a rise to above normal. At the higher dose there was a drop in NK activity, which remained down for the period of observation. This lack of augmentation, or even inhibition at higher doses of immune modulators has been noted often. These results are summarized in Figure 8.

Table 10. Comparison of interferon titers in male and female Rhesus monkeys.

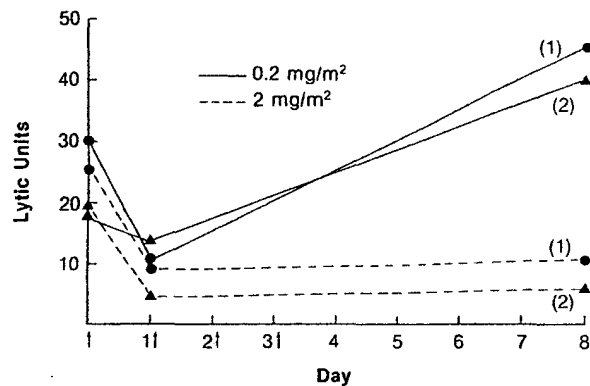| Sex	No.	Values are in I.U. per ml serum 8 Hour	24 hour
Male	1	3,200	200
	2	1,000	130
	3	4,000	200
Geom. Mean		2,339	173
Rel. S.E.		1.5	1.15
Female	1	250	5
	2	130	5
	3	630	10
Geom. Mean		274	6.3
Rel. S.E.		1.58	1.26
Male vs. Female		T = 3.72 d.f. = 4 p = 0.03	T = 12.2 d.f. = 4 p < 0.001

Figure 8. Effect of poly(ICLC) injection into monkeys on
natural killer cell activity in peripheral white
blood cells

Table 10 shows an interesting difference between male and female
monkeys with regard to the production of interferon. It can be seen that
male monkeys made significantly more interferon in response to a given
dose of poly(ICLC) than did female monkeys.

Studies in people were done as part of therapeutic trials in 29
multiple sclerosis patients, at NIH, Walter Reed and the U. of Texas in
Dallas (C. Bever, D. McFarlin, A. Salazar, R. Tyndall, H. MacFarland, and
H. Levy, manuscript in preparation), and in 59 cancer patients studied at
NIH and the Portsmouth Navel Hospital, (K. Foon, A. Malluish, J. Reed,
and H. Levy, unpublished observations). Most of the M.S. patients stabil-
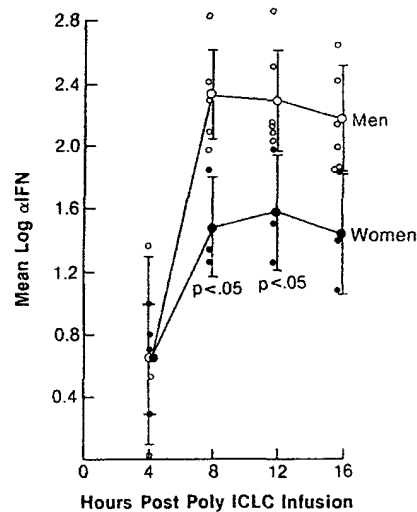ized for a while after the initiation of treatment.[10] Some declined,

Figure 9. Difference between men and women in amount of
interferon produced in response to injection of
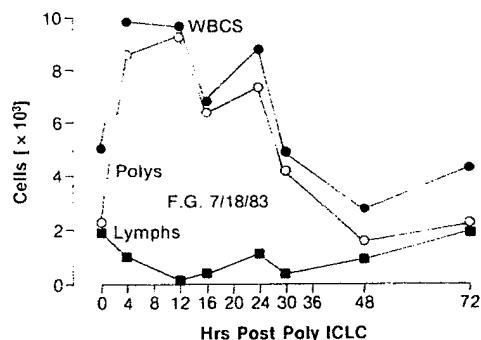poly(ICLC) (100 µg/kg), intravenously.

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Figure 10. Typical response of injection of poly(ICLC) (100
µg/kg) into man on white blood cells and subsets.

perhaps half, after 6-8 months. The remainder remained stable during the
period of treatment and observation.

Figure 9 shows that as with monkeys, men made more interferon in
response to a given dose of poly(ICLC) than did women. Hematologic
studies in M.S. patients showed acute changes in total wbc, as well as in
lymphocytes and granulocytes. Within 4 hours after injection, total wbc
increased. As with the monkeys at the higher dose, there was a marked
decrease in lymphocytes and an increase in polymorphonuclear leukocytes.
Figure 10 shows a typical reaction.

Lymphocytes remained depressed for 48 hours before returning to
normal. The rapid decrease and rapid recovery suggest strongly that the
changes are due to sequestering of the cells rather than destruction. All
these data resemble those just reported in monkeys.

Table 11. Changes in % monocytes in patients receiving
poly(ICLC).

Patient	Date	0 hours	24 hours	% Increase after 24 hours
F. G.	3/13/83	9.54	15.22	89
	6/22/83	9.44	8.95	- 5
	7/19/83	7.95	6.39	- 20
	2/06/84	13.1	17.8	36
V. T.	2/17/83	7.29	32.3	349
	3/09/83	8.29	31.5	280
A. P.	2/16/83	6.07	26.0	328
	3/15/83	19.8	24.7	25
	4/13/83	7.48	26.5	254
	12/06/83	3.30	14.7	354
C. W.	1/09/84	3.70	15.0	305
R. R.	7/12/83	13.2	22.9	73
T. B.	7/06/83	15.1	46.2	206

Table 12. NK activity in M.S. patients.

| | | 40:1 E:T Ratio % Specific Lysis | | | |
		0	24 Hrs	48 Hrs	%Change
AP	7/13	29	–	52	+79
TP	12/06	27	15	38	+30
FG	2/06	45	25	37	-18
TB	2/27	28	18	46	+64
AP	12/06	26	15	37	+42
FG	10/18	40	–	49	+23
TB	11/18	40	–	41	+ 3
TB	7/13	31	–	72	+132
Averages		33.3		46.5	

$$p < 0.01$$

There was an increase in monocyte antitumor activity and in the percent monocytes in the blood in all patient groups examined. Table 11 shows the changes in the %monocytes. Monocytes in blood are, of course, the analog of macrophages in tissues which, as seen earlier, were also

Table 13. Changes in OKT[3+] cells in patients receiving poly(ICLC).

Patient	Date	0 hours	24 hours
F.G.	3/30/83	68.2	56.9
	6/22/83	65.3	56.1
	7/19/83	62.7	57.7
	2/06/84	62.6	41.3
V.T.	2/17/83	65.1	58.8
	3/09/83	70.2	60.6
	3/06/84	75.3	55.1
A.P.	2/16/83	74.7	66.6
	3/15/83	63.4	33.6
	4/13/83	77.9	51.8
	11/01/83	78.0	66.5
	12/06/83	78.6	53.9
	1/10/84	76.1	56.5
H.T.	5/02/83	58.8	43.2
C.W.	1/09/84	70.7	40.5
	2/15/84	53.2	51.4
R.R.	7/12/83	73.8	64.0
T.B.	7/06/83	66.4	39.0
	11/08/83	67.8	68.7
	2/27/84	66.8	47.8

Table 14. Effect of poly(ICLC) on DR expression in M.S.
patients.

			%Cells Showing DR Time in Hrs. Post-treatment	
	Patient	Date	0 hours	24 hours
	FG	3/30	24.4	26.4
		6/22	26.7	28.6
		7/19	27.1	29.8
	VT	2/17	17.7	46.4
		3/09	26.5	39.7
	AP	2/16	16.5	36.8
		3/15	20.7	27.5
		4/13	15.2	33.9
	HT	5/02	19.6	38.7
	RR	7/12	25.1	29.9
	TB	7/06	31.4	31.4
	Averages		22.8	33.5
			$p < 0.001$	

elevated in the mouse. Natural killer cell activity in the peripheral
wbc, in the M.S. patients was depressed 24 hours after injection but
became elevated above the preinjection level by 48 hours, as shown in
Table 12. In the cancer patients, at the low dose of $1mg/m^2$ there was
some suggestion of elevation of NK cell activity, but there was a clear
cut depression at the higher ($4mg/m^2$) dose.

Table 15. Effect of poly(ICLC) on helper/suppresser ratios.

	Treatment Date	0 Time	24 Hrs.	% Increase
F.G.	3/30/83	2.66	7.28	174
	6/22/83	3.12	4.32	39
	7/19/83	2.78	4.89	76
V.T.	3/09/83	2.36	2.50	6
A.P.	2/16/83	2.05	3.10	51
	3/15/83	3.26	2.54	-22
	4/13/83	2.01	2.19	9
H.T.	5/02/83	1.46	2.26	55
R.R.	7/12/83	2.81	3.35	19
T.B.	7/06/83	1.65	3.61	119

There was also a transient decline in cells responding positively to the OKT3 reagent in the FACS assay. This is taken to be a measure of T cells. (Table 13) Changes were seen in a protein of the major histo-compatability locus, the DR antigen (Table 14) and also in Leu 11+ cells. Increased 2'5'A. synthetase activity was seen in all patients examined (Figure 11), even in those where no measurable interferon was found. Of particular interest in these days of concern with AIDS is the observation that the ratio of T helper cells (the T4 cells) to T suppresser (T8) cells, a measure that is depressed in AIDS patients, is elevated after injection with poly(ICLC). Table 15 shows some data to this effect in a group of multiple sclerosis patients. Table 16 shows the same phenomenon in one patient who was reportedly tested for this effect.

A number of the changes seen may reflect, at least in part, transient removal of specific wbc subsets from the blood stream, with sequestration into lymph nodes. This sequestration has been examined in greater detail in rats where the accumulation of lymphocytes into nodes after poly(ICLC) injection has been visualized. The extent of accumulation is proportional to the dose of poly(ICLC) given. As reported elsewhere, poly(ICLC) induces the production of increased levels of cortisol in people.[10] Some of the changes mentioned above are consistent with the effects that cortisol can bring about.

A few words about toxicity in humans should be inserted here. The original phase-1 toxicity study,[11] used the approach that was then standard with oncologists, namely determine what is the maximum tolerated dose (mTD), and then treat patients with that dose. In that study, 12 mg/m² i.v. was found to be the mTD. Subsequent trials, particularly with very ill patients found this dose to be excessively toxic. Fevers up to 104°F, severe myalgia and arthralgia were experienced. At this time it was determined from the mouse, monkey and human studies just summarized that high doses do not maximize immune enhancement and may actually be inhibitory. These earlier studies inadvertently were using doses that maximized toxicity and minimized effectiveness. Current studies range from 0.250 mg/m²i.v. in cancer patients to 3 mg/m² intramuscularly in M.S. patients. Side effects consist of a mild myalgia, with fever up to 99.5°F. The M.S. patients are being treated on an outpatient basis.

Table 16. Changes in OKT4/OKT8 ratio with repeat tests in one patient.

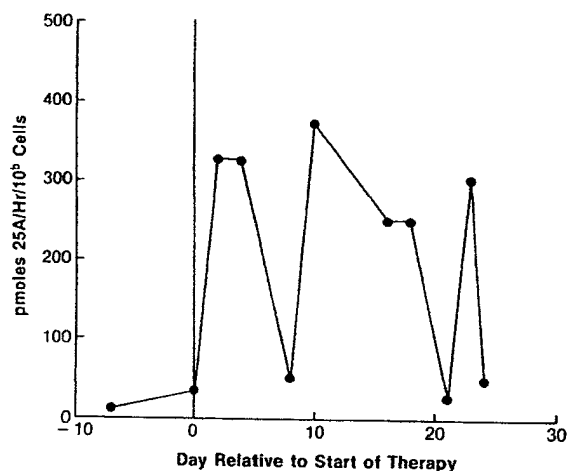| Date	0 hours	24 hours	% Increase
2/16/83	2.05	3.10	51
3/09/83	2.36	2.50	6
3/15/83	3.26	2.54	−22
3/30/J3	2.66	7.28	174
4/13/83	2.01	2.19	9
5/02/83	1.46	2.26	55
6/22/83	3.12	4.32	39
7/06/83	1.65	3.61	119
7/12/83	2.81	3.35	19
7/19/83	2.78	4.89	76

Figure 11. Effect of poly(ICLC) (100 µg/kg) injection to humans on 2'5' *A. synthetase.*

In summary, the injection of poly(ICLC) into primates, both monkeys and people, produces a number of changes in hematology and in immune reactivity, most of which are enhanced at low doses. Higher doses may actually lead to inhibition in some cases. Of particular interest is the observation that there is an elevation in the ratio of T-helper to T-suppresser cells. This poly(ICLC)-induced change plus its enhancement of monocyte and NK cell activity, and its antiviral activity, suggest that it should be considered for trial as a therapeutic agent in AIDS. The ability to elicit specific cytotoxic T cells might indicate potential usefulness as an adjuvant with AIDS vaccine.

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